PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SP-P2093PC00	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2005/051244	International filing date *(day/month/year)* 17.03.2005	Priority date *(day/month/year)* 19.03.2004
International Patent Classification (IPC) or national classification and IPC C07D209/20, C07D417/12, C07D401/12, C07D403/12, C07D405/12, C07D409/12, C07C237/22, A61P9/12, A61K31/405		
Applicant SPEEDEL EXPERIMENTA AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08.11.2005	01.03.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Cortés, J Telephone No. +49 89 2399-8206

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/051244

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-47 as originally filed

   Claims, Numbers

   1-10 received on 11.11.2005 with letter of 08.11.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 10

because:

☒ the said international application, or the said claims Nos. 10 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
   - ☐ complied with.
   - ☒ not complied with for the following reasons:

     see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
   - ☒ all parts.
   - ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 10 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion with regard to the industrial applicability will be formulated for this claim (Article 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

The present application lacks unity of invention according to Rule 13.1 to 13.3 PCT, since different separate groups of inventions are claimed which are not linked by a single general inventive concept.

These groups are:

1 compounds of option (A)
2 compounds of option (B)
3 compounds of option (C)

The problem of the invention was the provision of new renin inhibitors for the treatment of hypertension.

D1 to D4 disclose compound groups with which the present groups of invention overlap substantially, and which are renin inhibitors for the treatment of hypertension.

New compounds of group 1 seem to differ from the structurally closest examples of the prior art in the hydroxy group of the methylene linker X.

New compounds of group 2 seem to differ from the structurally closest examples of the prior art in that the ring of R1 which is not directly bonded to X is substituted.

New compounds of group 3 seem to differ from the structurally closest examples of the

prior art in the choice of specific heterocycles for the substituent R1.

Amongs these groups of inventions there seems to be no common inventive concept, i.e. no unifying structural feature representing a contribution to the prior art.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents have been cited in the International Search Report:

D1: EP-A-0 678 503 (NOVARTIS) 25 October 1995 (1995-10-25)
D2: WO 03/103653 A (ELAN) 18 December 2003 (2003-12-18)
D3: EP-A-0 678 514 (NOVARTIS) 25 October 1995 (1995-10-25)
D4: EP-A-0 678 500 (NOVARTIS) 25 October 1995 (1995-10-25)
D5: EP-A-0 716 077 (NOVARTIS) 12 June 1996 (1996-06-12)
D6: EP-A-0 702 004 (NOVARTIS) 20 March 1996 (1996-03-20)

Novelty (Article 33(2) PCT)

The documents D1 and D2 discloses generic formulae wherein R1 is an optionally substituted alkylendioxybenzene, a condensed polyarene or a tetrahydronaphthalene (D1: e.g. page 3, formula (I), line 45) as well as specific compounds wherein R1 is (substituted) benzodioxine, benzodioxol and naphthalene (D1: e.g. page 40, example 4; page 51-52, example 46; page 53, examples 56-59; page 101, claim 25, line 3; page 102, claim 25, line 29, lines 49-56).

The meanings X is methylene and hydroxymethylene have been specifically disclosed in D1 and D2 (D1: e.g. claim 1).

D1 and D2 seem to disclose essentially the same compounds and generic formulae.

D3 and D4 disclose generic formulae which are encompassed by the present claim 1 (e.g. D3: R1 is an aromatic or a heteroaromatic residue; e.g. page 5, formula (Iia) and (IIb)).

It seems to have been the Applicant's intention to exclude exemplified prior art compounds by defining three compound groups which substantially overlap with the scope of D1 to D4, but which exclude exemplified compounds. However, the overlap of the three defined compound groups with the generic groups disclosed in D1 to D4 is not a novel selection, since these compound groups lack a new particular specific structural feature or combination of features. E.g. if the present option (A) is regarded: the feature "X is hydroxymethylene" as well as specific examples for "R1 is heterocyclyl" and "R1 is a polycyclic radical" have been specifically disclosed e.g. in D1 and D2. None of these features can therefore represent a contribution to the prior art.

The present claim set is therefore not novel.

The present compounds differ from the compounds in D5 and D6 in the definition of X.

Inventive Step (Article 33(3) PCT)

D1 to D6 disclose renin inhibitors for the treatment of hypertension. D1 could be regarded as the closest prior art.

The problem of the invention was the provision of new renin inhibitors for the treatment of hypertension.

Since D1 discloses a generic group which overlaps with the present generic group, compounds which would be within the claimed scope if they had not been excluded by provisos, as well as their alleged pharmacology and medical use, the present claim set lacks an inventive step.

Clarity (Article 6 PCT)

The Examiner disagrees with the Applicant's view that a skilled person would unambiguously understand the term "unsaturated hydrocarbon radical" as encompassing aromatic compounds. This should have been clarified in the claims.

The Applicant has amended the term "prodrug" in claim 1 by a functional definition. The

problem is not that the term "prodrug" as such is unclear, but the term "prodrug" in combination with a structural formula renders the structural information contained in the formula and the substituent definition ambiguous. E.g. some structurally related examples in D1-D6 could be transformed in-vivo to structurally defined compounds of the present invention and therefore be "prodrugs" of the present compounds.

The claimed scope is therefore unclear because of the term "prodrug" and its amended functional definition.